(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2001 (27.12.2001)

PCT

(10) International Publication Number
WO 01/98304 A1

(51) International Patent Classification[7]: C07D 487/04

(21) International Application Number: PCT/KR01/00819

(22) International Filing Date: 18 May 2001 (18.05.2001)

(25) Filing Language: Korean

(26) Publication Language: English

(30) Priority Data:
2000/34966 23 June 2000 (23.06.2000) KR

(71) Applicant *(for all designated States except US)*: **DONG A PHARM. CO., LTD.** [KR/KR]; 252 Yongdoo-dong, Dongdaemoon-ku, Seoul 130-070 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **YOO, Moo-Hi** [KR/KR]; #5-801 Woosung 3 cha Apt., 652, Gaepo 1-dong, Kangnam-ku, Seoul 135-241 (KR). **KIM, Won-Bae** [KR/KR]; #A-1801 Daelim Acrovil, Dokok-dong, Kangnam-ku, Seoul 135-240 (KR). **CHANG, Min-Sun** [KR/KR]; 6-1, Makok-ri, Namsa-myeon, Yongin-si 449-880 (KR). **KIM, Soon-Hoe** [KR/KR]; #316-702 Dongshin Apt., Chongmyeongmaeul, 956-2, Yongtong-dong, Paldal-ku, Suwon-si 442-470 (KR). **KIM, Dong-Sung** [KR/KR]; #501-903 Jookong Apt., Chamsil-dong, Songpa-ku, Seoul 138-220 (KR). **BAE, Chul-Jun** [KR/KR]; #307, 196-108, Bongchun 11-dong, Kwanak-ku, Seoul 151-061 (KR). **KIM, Yong-Duck** [KR/KR]; #503-201 Jookong Apt., Shinnamoosil, Yongtong-dong, Paldal-ku, Suwon-si 442-470 (KR). **KIM, Eun-Ha** [KR/KR]; 102-23, Sungnam-dong, Jungwon-ku, Sungnam-si 462-130 (KR).

(74) Agent: **LEE, Won-Hee**; 8th Fl., Sung-ji Heights II, 642-16 Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/98304 A1

(54) Title: A PROCESS FOR PREPARING PYRAZOLOPYRIMIDINONE DERIVATIVES FOR THE TREATMENT OF IMPOTENCE

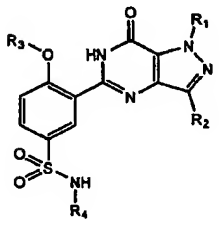
(57) Abstract: The present invention relates to the method for preparing pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts having efficacy on the treatment of impotence, one of male sexual dysfunctions. The method according to the present invention comprises the steps of chlorosufonation the pyrazolamide, followed by amination with amine and intramolecular cyclization. The method provides the pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts with high yield and in an economic manner.

A PROCESS FOR PREPARING PYRAZOLOPYRIMIDINONE DERIVATIVES FOR THE TREATMENT OF IMPOTENCE

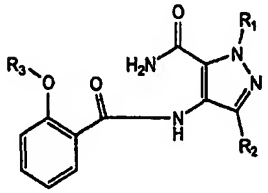
TECHNICAL FIELD

The present invention relates to a process for preparing pyrazolopyrimidinone derivatives of formula 1 and pharmaceutically acceptable salts thereof which have an efficacy on impotence, comprising the steps of chlorosulfonation of pyrazolamide compounds of formula 2, followed by amination with a primary amine and intramolecular cyclization.

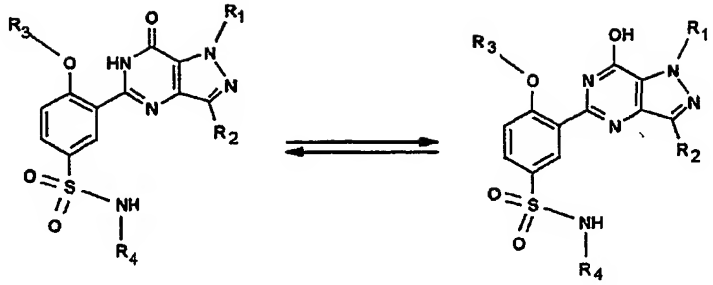
Formula 1



Formula 2



The compounds of formula 1 may exist in tautomeric equilibrium as shown below.



The compounds of formula 1 may also contain asymmetric centers and thus they can exist as enantiomers. The present invention includes both racemic mixture and separate individual enantiomers.

BACKGROUND ART OF THE INVENTION

Male erectile dysfunction is one of the most common sexual dysfunctions in man. Although erectile dysfunction can be primarily psychogenic in origin, it often accompanies chronic illnesses, such as diabetes mellitus, heart disease and a variety of neurological diseases. It is estimated that about 2 ~ 7% of the male population are impotent. Its prevalence is strongly related to age. For example, 18 ~ 75% of the age group of 55 to 80 years is believed to be impotent.

Various treatment options for erectile dysfunction are available, such as counseling, hormone replacement therapy, self-injection or transurethral application of vasodilator agents, vacuum devices, and vascular surgery. However, these therapeutic options have several limitations

such as side effects, high cost and low efficacy.

Recently, Sildenafil has been developed as a therapeutic agent for male erectile dysfuction by oral administration. Sildenafil is the first in a new class of drugs known as inhibiting phosphodiesterase-5 enzyme distributed specifically in corpus cavernosal tissues and induces relaxation of the corpus cavernosal smooth muscle cells, so that blood flow to the penis is enhanced, leading to an erection. Sildenafil has shown a response rate of around 80% in men with erectile dysfunction of organic cause.

Since sildenafil has been developed, various compounds for inhibiting phosphodiesterase-5 have been reported. Among them, pyrazolopyrimidinone compounds of formula 1 (KR Pat. No. 99-49384) were reported having better potency than that of sildenafil, based on the mechanism of inhibiting phosphodiesterase-5 and having better selectivity over phosphodiesterase-6 distributed in retina and phosphodiesterase-3 distributed in heart to reduce the side effects. Further, the pyrazolopyrimidinone compounds of formula 1 were said to be improved the solubility and the metabolism in the liver, which are very important factor affecting the rate of the absorption when administered orally.

The KR patent No. 99-49384 also disclosed a process for preparing the pyrazolopyrimidinone compounds of formula

1, comprising the steps of:

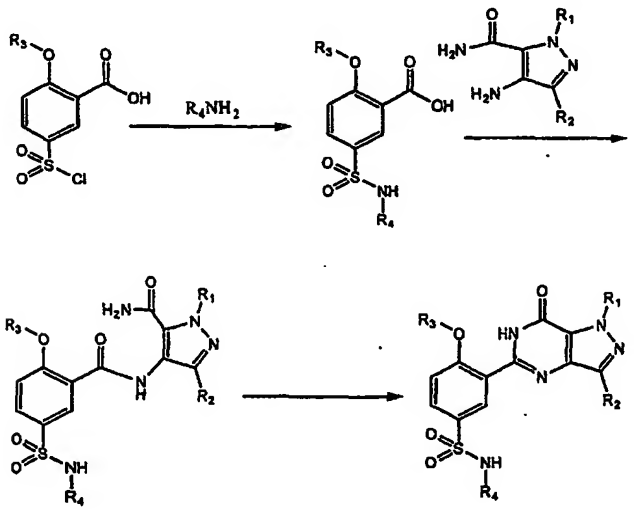
a) reacting chlorosulfonated alkoxy bonzoic acid with a primary amine to obtain sulfonamide-substituted benzoic acid;

b) reacting the obtained sulfonamide-substituted benzoic acid with pyrazolamine in the presence of activating reagent of carboxylic group or coupling agent of carboxylic group with amine group to obtain corresponding amide compound; and,

c) performing an intramolecular cyclization of the obtained amide compound to obtain the pyrazolopyrimidinone compound of formula 1.

This reaction is represented in scheme 1.

Scheme 1



However, the said process has several disadvantages. First, the reaction of the sulfonamide-substituted benzoic

acid with pyrazolamine in the step b) requires the expensive coupling reagent or activation reagent such as trichloro benzoyl chloride and EEDQ (N-ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline). Second, the yield of the step a) in which the chlorosulfonated alkoxy bonzoic acid reacts with a primary amine to produce sulfonamide-substututed benzoic acid is somewhat low, and thus, reduces the total yield of the process.

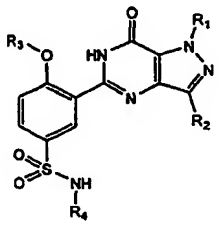
Leading to the present invention, the intensive and thorough research for efficiently preparing the pyrazolopyrimidinone compound useful for the treatment of impotence, carried out by the present inventors aiming to avoid the problems encountered in the prior arts, resulted in the finding that the pyrazolopyrimidinone compound can be prepared under mild condition in high yield, with high purity and in a economic manner by chlorosulfonation, amination with a primary amine and intramolecular cyclization of a pyrazolamide compound obtained by the reaction of alkoxy benzoic acid with pyrazolamine.

Therefore, it is an object of the present invention to provide a process for preparing pyrazolopyrimidinone derivatives of formula 1 and pharmaceutically acceptable salts thereof.

DISCLOSURE OF THE INVENTION

The present invention provides a process for preparing pyrazolopyrimidinone derivatives of formula 1 and pharmaceutically acceptable salts therof.

Formula 1



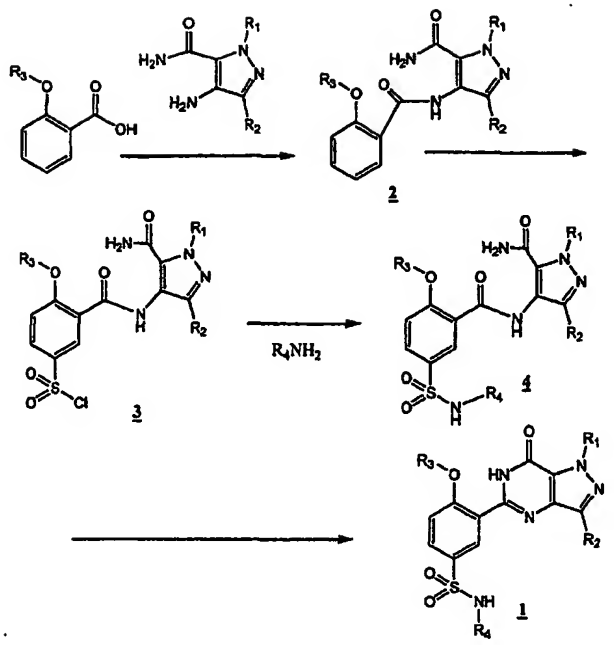
Referring to scheme 2, the process according to the present invention comprises the steps of:

a) chlorosulfonating a pyrazolamide compound of formula 2 to obtain a chlorosulfonated compound of formula 3;

b) reacting the chlorosulfonated compound of formula 3 with a primary amine to obtain a sulfonamide compound of formula 4; and,

c) performing an intramolecular cyclization of the sulfonamide compound of formula 4 to produce the compound of formula 1.

Scheme 2



Wherein,

R_1 represents hydrogen, C_1-C_6 alkyl, C_1-C_3 alkyl fluoride or C_3-C_6 cycloalkyl;

R_2 represents hydrogen, substituted or unsubstituted C_2-C_6 alkyl, C_1-C_3 alkyl fluoride or C_3-C_6 cycloalkyl;

R_3 represents substituted or unsubstituted C_1-C_6 alkyl, C_1-C_6 alkyl fluoride, C_3-C_6 cycloalkyl, C_3-C_6 alkenyl or C_3-C_6 alkynyl; and,

R_4 represents substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_1-C_9 alkenyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted benzene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazol, oxazole, piperidine,

morphorine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl.

As a substituent of R_2, R_3 and R_4, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, halogen, C_1-C_6 alkyl fluoride, C_1-C_{10} alkyloxy, substituted or unsubstituted bezene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazole, oxazole, piperidine, morphorine, imidazole, pyrrolidine, thienyl, triazole, pyrrole, and furyl can be mentioned.

Preferably, R_1 represents C_1-C_3 alkyl; R_2 represents substituted or unsubstituted C_2-C_6 alkyl; R_3 represents substituted or unsubstituted C_2-C_6 alkyl; R_4 represents substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted bezene, substituted or unsubstituted pyridine, or substituted or unsubstituted pyrrole, wherein the substituent of R_2, R_3 and R_4 is halogen, substituted or unsubstituted benzene, substituted or unsubstituted heterocycle selected from the group consisting of pyridine, pyrrolidine, piperidine, pyrrole, and substituted or unsubstituted C_3-C_6 cycloalkyl.

More preferably, R_4 represents substituted C_1-C_6

alkyl, wherein the substituent is pyrrolidine.

Particularly preferred are as follows:

(1) 5-[2-propoxy-5-(1-methyl-2-pyrrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one;

(2) 5-[2-propoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one; and

(3) 5-[2-propoxy-5-(2-pyridylmethyl amidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one.

Hereinafter, a detailed description will be given of the method of the present invention according to each step.

I. Chlorosulfonation Step (step a)

4-(2-alkoxy benzamido)-1-alkyl-3-alkyl-5-carbamoyl pyrazole of formula 2 is directly reacted with chlorosulfonic acid or reacted with a mixture of chlorosulfonic acid and suitable amounts of thionyl chloride at an appropriate temperature, 20 °C or lower, to prepare the chlorosulfonated compound of formula 3.

II. Sulfonamidization Step (step b)

The obtained chlorosulfonated compound is reacted

with a primary amine in an appropriate solvent at suitable temperature, to produce the sulfonamide compound of formula 4.

The solvent which can be used in this reaction includes alcohol, dichloromethane and chloroform, but not limited thereto. The skilled in the art would adapt an appropriate solvent in the consideration of the solubility of the starting material, reaction condition, etc.

As a primary amine used, 2-(2-aminoethyl)-1-methylpyrrolidine, 3-aminomethyl-1-methylpyrrolidine or 2-aminomethyl-pyridine can be preferably mentioned. The amount of the primary amine used in this reaction is no less than 2 equivalents based on the chlorosulfonated compound. Alternatively, when acid scavenger such as tertiary amine, which scavenging the acid generated during the reaction, is used, the primary amine can be used in a stoichiometric quantity.

The reaction temperature of this reaction is preferably 20 °C or lower. The sulfonamide compound of formula 4 can be worked up from the reaction mixture and proceeded to the next reaction step c). Or step c) can be performed in situ by just adding a suitable base to the

reaction mixture in situ without workup.

III. Intramolecular Cyclization Step (step c)

Pyrazolopyrimidinone of formula 1 is prepared through intramolecular cyclization of the sulfonamide compound of formula 4. The intramolecular cyclization is carried out in the presence of a suitable base at the appropriate temperature. For example, metal salts of alcohol, metal salts of ammonia, amine, alkali or alkali earth metal hydrides, hydroxides, carbonates, bicarbonates, and bicyclic amidines such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) can be mentioned as a suitable base.

The solvent which can be used in the intramolecular cyclization includes alcohol such as methanol, ethanol, isopropanol and t-butanol; ether including tetrahydrofuran, dimethoxyethane and dioxane; aromatic hydrocarbons, such as benzene, toluene, xylene, chloro benzene; acetonitrile, dimethylsulfoxide, dimethylformamide, N-methylpyrrolidin-2-one and pyridine.

The present invention provides the sulfonamide compound of formula 4 from step a) and step b) reaction in good yield and in high purity. And as previously mentioned, the step c) can be performed in situ with the

sulfonamide compound of formula 4 produced in the step b) in a one-pot reaction, thereby reducing the overall procedure of the reaction and effectuating the efficient synthesis of pyrazolopyrimidinone compound of formula 1.

In particular, according to the preferred embodiment of the present invention, even though tertiary amine was used as a part of substituent of R_4, the yield of the reaction was high.

The present invention also provides a method for preparing pharmaceutically acceptable salts of pyrazolopyrimidinone compound as represented in formula 1, wherein the pharmaceutically acceptable salts of pyrazolopyrimidinone compound can be prepared by adding a pharmaceutically acceptable free acid to the pyrazolopyrimidinone compound of formula 1. Examples of a free acid include inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and so on; and organic acids, for example, citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, p-toluenesulfonic acid, galacturonic acid, glutamic acid, or aspartic acid.

A better understanding of the present invention may be obtained in light of the following examples which are set forth to illustrate, but are not to be construed to limit the present invention.

EXAMPLE

Molecular structures of the present compounds were confirmed by infrared spectrometry, ultraviolet spectrometry, nuclear magnetic resonance spectrometry, mass spectrometry, and elemental analysis of representative compounds by comparing calculated values with observed values.

The pyrazolamide compound of formula 2, which is a starting material of the present invention, can be obtained in high yield by reacting alkoxy benzoic acid with pyrazolamine as illustrated in the scheme 2.

<Preparation> Preparation of 4-[2-propoxy benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

To a solution of 25 g of 2-propoxy benzoic acid dissolved in dichloromethane, 66 g of thionyl chloride was added and stirred for 3 hours under reflux. After reaction was completed, the solvent and excessive thionyl chloride were distilled off under reduced pressure. To the residue was added 200 ml of dichloromethane (reaction solution 1). In another container, to 24 g of 1-methyl-3-

propyl-4-amino-5-carbamoyl pyrazole in dichloromethane was added 13.4 g of triethylamine and 100 mg of dimethylaminopyridine and then cooled to 0°C, to which said reaction solution 1 was slowly added while maintaining the temperature of the solution at 0°C, and then stirred for 1 hour. The reaction mixture was successively washed with water, saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to obtain a crude product and then triturated with hexane to give 39 g of the title compound.

^{1}H NMR($CDCl_3$) : 0.91(t,3H), 1.05(t,3H), 1.62(m,2H), 1.89(m,2H), 2.52(t,2H), 4.06(s,3H), 4.18(t,2H), 5.57(br s,1H), 7.09(m,2H), 7.52(m,1H), 7.73(br s,1H), 8.26(dd,1H), 9.45(br s,1H)

<Example 1A> Preparation of 5-[2-propoxy-5-(1-methyl-2-pyrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

(Step a) preparation of 4-[2-propoxy-5-(chlorosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

To 23 ml of chlorosulfonic acid cooled to 0°C, 10 g of 4-[2-propoxy benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole was added and then stirred at room temperature

for 2 hours. Reaction mixture was added to ice water of 0 °C and then stirred for 1 hour to obtain white solid, which was filtered and washed with water. The obtained white solid was dissolved in ethyl acetate. The solution was successively washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain a crude product and triturated with hexane to give 9.14 g of the title compound.

^{1}H NMR($CDCl_3$) : 0.92(t,3H), 1.08(t,3H), 1.62(m,2H), 1.97(m,2H), 2.50(t, 2H), 4.04(s,3H), 4.32(t,2H), 5.63(br s,1H), 7.24(d,1H), 7.54(br s, 1H), 8.15(dd,1H), 8.93(d,1H), 9.17(br s,1H)

(Step 2) preparation of 4-[2-propoxy-5-(1-methyl-2-pyrolidinylethyl amidosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

To 9.14 g of 4-[2-propoxy-5-(chlorosulfonyl) benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole in dichloromethane, 5 ml of 2-(2-aminoethyl)-1-methyl pyrrolidine was added at 0°C and stirred for 1 hour at room temperature. After completion of reaction, the reaction solution was diluted with dichloromethane. The solution was successively washed with saturated sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The

filtrate was concentrated under reduced pressure to produce a crude product and triturated with a mixture of hexane:ethyl acetate (10:1) to give 9.69 g of the pure title compound.

^{1}H NMR($CDCl_3$) : 0.90(t,3H), 1.06(t,3H), 1.59(m,2H), 1.70(m,6H), 1.93(m, 2H), 2.15(m,1H), 2.29(s,3H), 2.39(m.1H), 2.49(t,2H), 3.04(m,3H), 4.02(s,3H), 4.24(t,2H), 5.82(br s,1H), 7.13(d,1H). 7.58(br s,1H), 7.96(dd,1H), 8.67(d,1H), 9.26(br s,1H)

(Step 3) preparation of 5-[2-propoxy-5-(1-methyl-2-pyrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

To a solution of 9.59 of 4-[2-propoxy-5-(1-methyl-2-pyrolidinylethyl amidosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole dissolved in 192 ml of t-butanol, 4.02 g of potassium t-butoxide was added and then stirred for 8 hours under reflux. After completion of reaction, the reaction solution was cooled to room temperature and diluted with ethyl acetate. The solution was successively washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was vacuum-distilled to remove the solvent. Column chromatography of the residue on silica gel gave 7 g of the pure title compound.

^{1}H NMR($CDCl_3$) : 0.99(t,3H), 1.15(t,3H), 1.56(m,4H),

1.79(m,4H), 2.02(m,3H), 2.28(s,3H), 2.36(m,1H), 2.89(t,2H), 3.07(m,3H), 4.23(t,2H), 4.24(s,3H), 7.11(d,1H), 7.92(dd,1H), 8.88 (d,1H)

<Example 1B> Preparation of 5-[2-propoxy-5-(1-methyl-2-pyrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

(Step 1) preparation of 4-[2-propoxy-5-(chlorosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

To 32.8 ml of chlorosulfonic acid cooled to 0 °C, 8.48 ml of thionyl chloride and 20 g of 4-[2-propoxy benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole were successively added dropwise and portionwise, and then stirred for 2 hours at room temperature. Reaction mixture was added to ice water of 0 °C. After 1 hour, the reaction mixture was extracted with ethyl acetate. The organic solution was successively washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain a crude product and triturated with a mixture of hexane:ethyl acetate (10:1) to give 23 g of the title compound.

^{1}H NMR($CDCl_3$) : 0.92(t,3H), 1.08(t,3H), 1.62(m,2H), 1.97(m,2H), 2.50(t, 2H), 4.04(s,3H), 4.32(t,2H), 5.63(br s,1H), 7.24(d,1H), 7.54(br s, 1H), 8.15(dd,1H), 8.93(d,1H), 9.17(br s,1H).

(Steps 2 and 3) preparation of 5-[2-propoxy-5-(1-methyl-2-pyrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

To 20.8 g of 4-[2-propoxy-5-(chlorosulfonyl) benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole in ethanol, 11.3 ml of 2-(2-aminoethyl)-1-methyl pyrrolidine was added at 0 °C and stirred for 1 hour at room temperature. To this solution, 12 g of sodium ethoxide was added and stirred for 5 hours under reflux. After completion of reaction, the reaction solution was cooled to room temperature and adjusted to pH 9 by concentrated hydrochloric acid. The reaction solution was diluted with dichloromethane. The solution was successively washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to remove the solvent, which was then recrystallized with ethanol to give 18.4 g of the pure title compound.

^{1}H NMR($CDCl_3$) : 0.99(t,3H), 1.15(t,3H), 1.56(m,4H), 1.79(m,4H), 2.02(m,3H), 2.28(s,3H), 2.36(m,1H), 2.89(t,2H), 3.07(m,3H), 4.23(t,2H), 4.24(s,3H), 7.11(d,1H), 7.92(dd,1H), 8.88 (d,1H).

<Example 2> Preparation of 5-[2-propoxy-5-(1-methyl-3-pyrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-

propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

(Step 1) preparation of 4-[2-propoxy-5-(chlorosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

The title compound was produced in the same manner as in the step 1 of the above example 1B.

(Step 2) preparation of 4-[2-propoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

To 1.0 g of 4-[2-propoxy-5-(chlorosulfonyl) benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole in dichloromethane, 516 mg of 3-aminomethyl-1-methyl pyrrolidine was added at 0 °C and stirred for 1 hour at room temperature. After completion of reaction, the reaction solution was diluted with dichloromethane. The solution was successively washed with saturated sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product and triturated with hexane to give 825 mg of the pure title compound.

^{1}H NMR($CDCl_3$) : 0.91(t,3H), 1.06(t,3H), 1.60(m,3H), 1.99(m,3H), 2.34(s, 3H), 2.40(m,6H), 2.85(m,1H), 2.94(d.2H), 4.03(s,3H), 4.24(t,2H), 5.82(br s,1H), 7.13(d,1H). 7.58(br s,1H), 7.99(dd,1H), 8.88(d,1H),

9.29(br s,1H).

(Step 3) preparation of 5-[2-propoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

To a solution of 825 mg of 4-[2-propoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl) benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole dissolved in 10 ml of t-butanol, 213 mg of potassium t-butoxide was added and then stirred for 8 hours under reflux. After completion of reaction, the reaction solution was cooled to room temperature and diluted with dichloromethane. The solution was successively washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to remove the solvent. Column chromatography of the crude product on silica gel gave 719 mg of the pure title compound.

^{1}H NMR($CDCl_3$) : 1.00(t,3H), 1.16(t,3H), 1.60(m,1H), 1.82(m,2H), 2.02(m,3H), 2.38(s,3H), 2.50(m,4H), 2.90(t,2H), 3.01(d,2H), 4.23(t,2H), 4.25(s,3H), 7.12(d,1H), 7.94(dd,1H), 8.88 (d,1H).

<Example 3> Preparation of 5-[2-propoxy-5-(2-pyridylmethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

(Step 1) preparation of 4-[2-propoxy-5-(chlorosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

The title compound was prepared in the same manner as in the step 1 of the above example 1B.

(Step 2) preparation of 4-[2-propoxy-5-(2-pyridylmethyl amidosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole

To 1.0 g of 4-[2-propoxy-5-(chlorosulfonyl) benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole in dichloromethane, 0.47 ml of 2-aminomethyl-pyridine was added at 0 °C and stirred for 1 hour at room temperature. After completion of reaction, the reaction solution was diluted with dichloromethane. The solution was successively washed with saturated sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to furnish a crude product and triturated with hexane to give 955 mg of the pure title compound.

^{1}H NMR($CDCl_3$) : 0.90(t,3H), 1.05(t,3H), 1.59(m,2H), 1.90(m,2H), 2.49(t, 2H), 2.65(br s,1H), 4.02(s,3H), 4.25(t,2H), 4.28(d,2H), 5.79(br s,1H), 6.28(t,1H), 7.09(d,1H). 7.26(d,1H), 7.16(m,1H), 7.61(m,1H), 7.99(dd,1H), 8.42(d,1H), 8.69(d,1H), 9.22(br s,1H).

(Step 3) preparation of 5-[2-propoxy-5-(2-pyridylmethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one

To a solution of 955 mg of 4-[2-propoxy-5-(2-pyridylmethyl amidosulfonyl)benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole dissolved in 12 ml of t-butanol, 244 mg of potassium t-butoxide was added and then stirred for 8 hours under reflux. After completion of reaction, the reaction solution was cooled to room temperature and diluted with ethyl acetate. The solution was successively washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to remove the solvent. The reidue was column chromatographed on silica gel to give 821 mg of the pure title compound.

^{1}H NMR($CDCl_3$) : 1.02(t,3H), 1.15(t,3H), 1.85(m,2H), 2.04(m,2H), 2.93(t,2H), 4.21(t,2H), 4.26(s,3H), 4.41(d,2H), 6.30(t,1H), 7.09(d,1H), 7.30(m,1H), 7.39(d,1H), 7.77(m,1H), 7.96(dd,1H), 8.45(d,1H), 8.86(d,1H), 10.82(br s,1H).

According to the present invention, pyrazolopyrimidinone derivatives of formula 1 can be prepared in high yield with high purity. In addition, the inexpensive reagents can be used such that they can be

prepared in an economic manner.

The present invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.

WHAT IS CLAIMED IS:

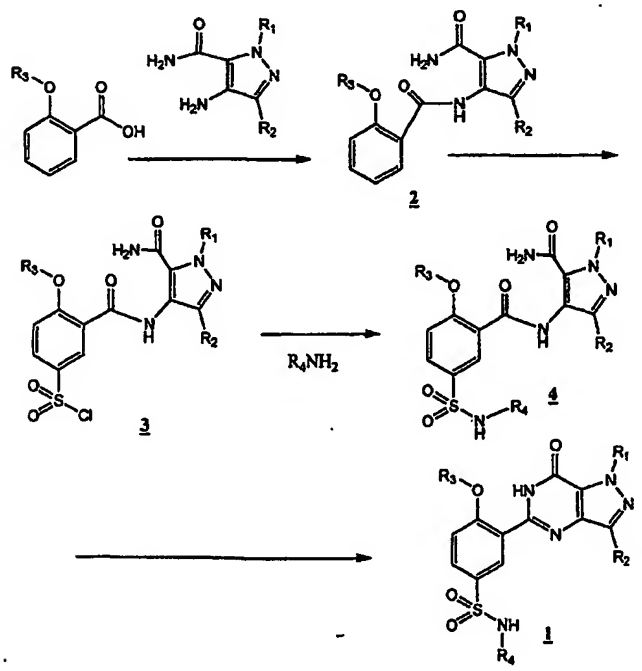
1. A method for preparing pyrazolopyrimidinone derivatives of formula 1, as represented in the following scheme 2, comprising the following steps of:

a) chlorosulfonating a pyrazolamide compound of formula 2 to obtain a chlorosulfonated compound of formula 3;

b) reacting the chlorosulfonated compound of formula 3 with a primary amine to obtain a sulfonamide compound of formula 4; and,

c) performing an intramolecular cyclization of the sulfonamide compound of formula 4 to produce the compound of formula 1.

Scheme 2



2. The method according to claim 1, wherein

R_1 represents hydrogen; C_1-C_6 alkyl; C_1-C_3 alkyl fluoride; or C_3-C_6 cycloalkyl,

R_2 represents hydrogen; substituted or unsubstituted C_2-C_6 alkyl; C_1-C_3 alkyl fluoride; or C_3-C_6 cycloalkyl,

R_3 represents substituted or unsubstituted C_1-C_6 alkyl; C_1-C_6 alkyl fluoride; C_3-C_6 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl, and

R_4 represents substituted or unsubstituted C_1-C_{10} alkyl; substituted or unsubstituted C_1-C_9 alkenyl; substituted or unsubstituted C_3-C_6 cycloalkyl; substituted or unsubstituted bezene; or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazol, oxazole, piperidine, morphorine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl,

in which, substituents usable for R_2, R_3 and R_4 comprises C_1-C_{10} alkyl; C_3-C_6 cycloalkyl; halogen; C_1-C_6 alkyl fluoride; C_1-C_{10} alkyloxy; substituted or unsubstituted bezene; or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan,

benzthiazole, pyrazole, thiadiazole, oxazole, piperidine, morphorine, imidazole, pyrrolidine, thienyl, triazole, pyrrole, and furyl.

3. The method according to claim 1, wherein

R_1 represents C_1-C_3 alkyl,

R_2 represents substituted or unsubstituted C_2-C_6 alkyl,

R_3 represents substituted or unsubstituted C_2-C_6 alkyl, and

R_4 represents substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted bezene, substituted or unsubstituted pyridine, or substituted or unsubstituted pyrrole,

in which, substituents usable for R_2, R_3 and R_4 comprises halogen, substituted or unsubstituted benzene, substituted or unsubstituted heterocycle selected from the group consisting of pyridine, pyrrolidine, piperidine, pyrrole, and substituted or unsubstituted C_3-C_6 cycloalkyl.

4. The method according to claim 1, wherein said derivative of formula 1 is selected from the group consisting of 5-[2-propoxy-5-(1-methyl-2-pyrrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one, 5-

[2-propoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d) pyrimidin-7-one, and 5-[2-propoxy-5-(2-pyridylmethyl amidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidin-7-one.

5. The method according to claim 1, wherein said step a) is carried out at about 20 °C or lower.

6. The method according to claim 1, wherein said step b) is carried out at about 20 °C or lower.

7. The method according to claim 1, wherein said step c) is performed in the presence of a solvent selected from the group consisting of alcohol, dichloromethane and chloroform.

8. The method according to claim 1, wherein said step c) is performed in the presence of a solvent selected from the group consisting of alcohols, ethers, aromatic hydrocarbons, acetonitrile, dimetylsulfoxide, dimethylformamide, N-methylpyrrolidin-2-one and pyridine.

9. The method according to claim 1, wherein said c) is performed in the presence of a base selected from the group consisting of metal salts of alcohols, metal salts

of ammonia, amines, alkali or alkali earth metal hydrides, hydroxides, carbonates, bicarbonates, and bicyclic amidines such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene).

10. A method for preparing salts of pyrazolopyrimidinone derivatives of formula 1 by reacting pyrazolopyrimidinone compounds with a free acid.

11. The method according to claim 10, wherein said free acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, p-toluenesulfonic acid, galacturonic acid, glutamic acid and aspartic acid.

INTERNATIONAL SEARCH REPORT

...ternational application No.
PCT/KR01/00819

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
IPC7: C07D

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
STN online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/27848(DONG A PHARM. CO. LTD.), 18. 05. 00; see page 16- page 18: claims, cited in the application	2-11
A	WO 98/49166(PFIZER LIMITED), 05. 11. 98; see page 13- page 17: claims	2-11
A	WO 93/06104(PFIZER LIMITED), 01. 04. 93; see page 4- page 7: claims	2-11
A	EP 463,756(PFIZER LIMITED), 02. 01. 92; see page 4- page 9: claims	2-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 SEPTEMBER 2001 (05.09.2001)	05 SEPTEMBER 2001 (05.09.2001)

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	LEE, Yu Hyung Telephone No. 82-42-481-5603

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/00819

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO A1 00/27848	18. 05. 00	AU A5 10817	29. 05. 00
WO A1 98/49166	05. 11. 98	AU A1 76445/98	24. 11. 98
		EP A1 977756	09. 02. 00
		GB A0 9708406	18. 06. 97
		NO A 995211	25. 10. 99
WO A1 93/06104	01. 04. 93	GB A0 9119704	30. 10. 91
		PT A 100862	30. 11. 93
EP A1 463,756	02. 01. 92	AU A1 79155/91	19. 03. 92
		CA AA 2044748	21. 12. 91
		CN A 1057464	01. 01. 92
		DE CO 69108991	24. 05. 95
		GB AO 9013750	08. 08. 90
		JP A2 6041133	15. 02. 94
		KR B1 9406628	23. 07. 94
		US A 5250534	05. 10. 93

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/00819

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to part of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 1 doesn't have the definitions for substitutents R1, R2, R3 and R4.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Search Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be established without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.